REMARKS/ARGUMENTS

I. Change of Attorney Docket No.:

Once again Applicants remind the Examiner that the Attorney Docket No. for the instant application has changed from 0630/1G704US2 to **36119.156US3**.

Applicants respectfully request that the Attorney Docket No. be updated on PAIR and that the Attorney Docket No. be used in any future correspondence relating to the instant application.

II. Information Disclosure Statement:

Applicants gratefully note that the Examiner has fully considered the references cited in the PTO-1449 form mailed May 31, 2005.

III. Status of the Claims:

Claims 12-24 and 26-42 are pending in the instant application.

Claims 12-24 were withdrawn from consideration pursuant to 37 C.F.R. § 1.142(b). Applicants note that the Examiner had previously indicated that when the claims drawn to the product are allowable, the process claims (claims 12-24) would be rejoined (*see,* Office Action of July 30, 2004, page 2, first paragraph).

Claims 26-42 are under examination in this application.

IV. Withdrawal of Prior Rejections:

Applicants gratefully acknowledge that the rejection of claims 35 and 39 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite has been withdrawn (*see,* Office Action, page 2, third paragraph).

Applicants also note that the rejection of claims 26-39 under 35 U.S.C. § 112, first paragraph, for purportedly not being enabling has been withdrawn by the Examiner (*see,* Office Action, page 2, fourth paragraph).

Applicants further note that the rejection of claims 26-40 under 35 U.S.C. § 112, first paragraph, for allegedly introducing new matter has also been withdrawn (*see,* Office Action, page 2, fifth paragraph).

V. **Rejections under 35 U.S.C. § 103(a):**

(i) Claims 26-27 and 30-40 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Calkhoven *et al.* (*Eur. J. Biochem.* **249**:113-120, 1997) in view of Ameis *et al.* (*J. Biol. Chem.* **265**:6552-6555, 1990), and further in view of Norris *et al.* (*J. Biol. Chem.* **270**:22777-22782, 1995) (*see,* Office Action, page 2, last full paragraph).

The sole independent claim in the instant application, claim 26, recites an isolated cell comprising (i) a first exogenous nucleic acid molecule which encodes an estrogen receptor; (ii) a second exogenous nucleic acid molecule which encodes a CCAAT/enhancer-binding protein (C/EBP) transcription factor; and (iii) a reporter gene operatively associated with a hepatic lipase (HL) promoter.

According to the Office Action, the primary reference (*i.e.,* Calkhoven *et al.*) allegedly teaches HepG2 recombinant cells containing three DNA constructs, namely: (i) a DNA construct expressing an estrogen receptor; (ii) a DNA construct expressing a transcription coactivator C/EBP; and (iii) a reporter construct linking the CAT reporter gene to the very low density apolipoprotein II (apoVLDL II) promoter (*see,* Office Action, page 4, first paragraph). The Office Action correctly notes that Calkhoven *et al.* do not teach a HL promoter or a luciferase reporter gene (*see,* Office Action, page 4, second paragraph).

The Office Action states that the secondary reference, Ameis *et al.*, purportedly teaches that the human HL promoter contains two CCAAT elements, and also *Alu* DNA repeats (*see,* Office Action, page 4, third paragraph).

Finally, the Office Action alleges that Norris *et al.* teaches an *Alu* consensus sequence that binds ER, as well as an assay system using luciferase. In addition, the Office Action purports that Norris *et al.* provides motivation to one of ordinary skill to screen ER responsive enhancers using a luciferase reporter gene (*see,* Office Action, page 4, fourth paragraph).

The Office Action alleges that it would have been obvious to one of ordinary skill to make and use a recombinant cell containing the claimed DNA constructs with a reasonable expectation of success by replacing the apoVLDL II promoter of the reporter of Calkhoven *et al.*, with the HL promoter of Ameis *et al.* to arrive at an estrogen-dependent HL promoter-driven reporter gene. The Office Action alleges that the skill in the art in making the claimed recombinant cell is very high and that one of ordinary skill would have been motivated to make and use an estrogen-dependent HL-promoter-driven reporter gene given that the *Alu* repeat of the HL promoter contains the consensus *Alu* sequence that binds ER as shown by Norris *et al.* (*see*, Office Action, page 6, first paragraph).

Applicants again respectfully assert that the pending claimed invention is non-obvious in view of the applied references for the reasons previously made of record (*see*, Amendment filed May 18, 2005, pages 9-14). There are at least two major reasons why the applied § 103 rejection is improper. Because these reasons do not seem to have been appreciated before, these reasons are rearticulated below for the Examiner's convenience.

First, the Federal Circuit has repeatedly stated that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *See, Tec Air Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999); and *In re Gordon, 733 F.2d 900, 221 USPQ 1125, 1127* (Fed. Cir. 1984). In the present context, the Examiner-cited primary reference, Calkhoven *et al.*, is directed to identifying the factors responsible for regulating the gene encoding the avian egg yolk precursor protein apoVLDL II. This reference is not interested, even peripherally, in studying the regulation of the HL gene. Therefore, if Calkhoven is modified as suggested by the Examiner, purportedly based on the teachings of Ameis and Norris, to replace the apoVLDL II promoter with the HL promoter, the suggested modification would render Calkhoven's reporter unsatisfactory for its intended purpose, *i.e.*, to study apoVLDL II regulation. For emphasis, Applicants reiterate that because the Federal Circuit has held that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, there is no suggestion or motivation to make the proposed modification, it is abundantly clear that

in the instant case there is simply no suggestion or motivation to modify Calkhoven as suggested by the Examiner to arrive at Applicants' claimed invention. Accordingly, Applicants respectfully assert that the Office Action has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that this rejection under § 103 be withdrawn.

In reply to the argument presented above, the Examiner responded that this argument was found unpersuasive and merely reiterated what the Examiner considered to be the teachings of each of the individual cited references (*i.e.*, Calkhoven, Ameis and Norris) (*see*, Office Action, page 3, last paragraph to page 5, first paragraph). This does not amount to a rebuttal of Applicants' arguments. Specifically, no reasoning has been advanced by the Office as to why the claimed invention is obvious in light of the holding by the Federal Circuit in *Tec Air Inc. v. Denso Mfg. Michigan Inc. (supra)*, and *In re Gordon (supra)*. Accordingly, Applicants respectfully request reconsideration of the above argument.

The second major reason for why the applied § 103 rejection is improper relates to the fact that none of the three references cited by the Examiner, taken alone or in combination, teach or suggest Applicants' claimed invention with any expectation of success. Specifically, the combined references do not teach, suggest, or provide motivation for an isolated cell comprising exogenous nucleic acid molecules encoding ER and C/EBP transcription factors, and an HL promoter-driven reporter.

The Office Action relies heavily on Ameis for introducing ER and C/EBP into a cell containing an HL reporter. Ameis *et al.* report that the human hepatic lipase gene 5'-nontranscribed region contains multiple cis-elements such as "TATA" box sequences, a hepatocyte-specific factor binding site "AGGTTAATTATTAAT," an element with homology to an "*Alu*" repeat sequence, two elements with homology to "CCAAT" elements, a cyclic AMP response element, and a glucocorticoid response element (*see*, Fig. 3 and page 6555, left column, first full paragraph). However, the Examiner provides no reasoning why the combined Examiner-cited references teach that the CCAAT element in the HL promoter of Ameis binds C/EBP and the Alu sequence binds ER. Simply, because C/EBP can bind CCAAT elements does not mean that all CCAAT sites actually bind C/EBP. That a cis-

element with homology or identity to known transcription factor binding sites exists in an upstream non-transcribed region, does not immediately imply that that site is bound by a transcription factor and/or that that site is involved in the functional regulation of the downstream gene. One of ordinary skill in the art would readily recognize that short cis-elements, like TATA or CCAAT, have a high probability of appearing frequently in a sequence the size of the 5' non-transcribed region of HL and that most of these occurrences would not correlate with functional activity. The role, if any, of any cis-elements with homology to known elements needs to be established by significant further experimentation. In fact, at the time of the filing of the instant application, CCAAT sites were known to bind proteins other than C/EBP, such as NF-Y, CTF, CP1, and CDP. Thus, a protein that is distinct from C/EBP may bind the CCAAT elements in the HL 5' non-transcribed region. The combined references cited by the Examiner do not teach or suggest which CCAAT binding factor, if any, binds the HL promoter. In fact, based on the C/EBP consensus sequence taught by Calkhoven, neither of the two CCAAT elements in Ameis' HL promoter would necessarily be expected to bind C/EBP (*see,* **Appendix A**). Similarly, the mere fact that a consensus Alu element that can bind ER is found in the HL gene upstream region does not automatically imply that ER binds this element. One of ordinary skill in the art at the time of filing this application was aware that the promoter context (*i.e.,* the arrangement of different cis-acting sequences in a regulatory sequence) is critical in determining which factors may bind to it and how they regulate that promoter. For example, if cis-elements A and B bind transcription factors X and Y in one promoter context, one cannot simply assume that the cis-elements A and B also bind X and Y when present in the context of a different regulatory region.

Even if we were to assume *arguendo* that the combined references taught that ER binds the Alu element and that C/EBP bound the CCAAT element in the HL promoter, the Examiner provides no reasoning for why one of ordinary skill in the art would choose the specific combination of C/EBP and ER to introduce into a cell with an HL-CAT reporter, when numerous other combinations of factors could be envisaged based on the promoter sequence provided by Ameis. For example, why not a cyclic AMP response element binding

factor and a glucocorticoid response element binding factor; or a cyclic AMP response element binding factor and an Alu element binding factor; or a glucocorticoid response element binding factor and a CCAAT element binding factor; or a hepatocyte-specific factor and an Alu element binding factor; or a glucocorticoid response element binding factor, a cyclic AMP response element binding factor and a hepatocyte-specific factor, etc. The Office Action has articulated no reasoning whatsoever why one of ordinary skill in the art would arrive at the specific combinations of Applicants' invention based on the combined references. Applicants respectfully assert that the Applicants' disclosure has been improperly used as a blueprint for piecing together the prior art to defeat patentability of Applicants' claimed invention.

In response to Applicant's arguments in the Amendment filed May 18, 2005, the Examiner noted that: (i) Applicants allegedly argued references individually and that one cannot show nonobviousness by attacking references individually where the rejection is based on combinations of references; and (ii) with respect to Ameis *et al.*, purported that the newly-cited reference, Voet *et al.* (John Wiley & Sons, 1990, page 865), indicates that undergraduate students had been taught that a promoter containing CCAAT sites would work 20 years before the effective filing date of the instant application (*see,* Office Action, page 5, second and third paragraphs).

Applicants disagree with the Examiner's characterization of Applicants' arguments. First, Applicants note that they are fully aware that one cannot show nonobviousness by attacking references individually where the rejection is based on combinations of references. It is incorrect that Applicants argued references individually (*see,* for example, page 8, last paragraph of Amendment filed May 18, 2005). Applicants have discussed each of the references to articulate why there is no motivation to combine the references, in the same way that the Examiner's Office Action attempts to discuss each reference in presenting the case for the § 103 rejection (*see,* Office Action, page 4).

Second, with respect to Voet, Applicants agree that CCAAT sequences were known prior to Applicants' filing date. However, the issue is not whether CCAAT sequences were known, but rather whether all occurrences of CCAAT sequences in a regulatory region

correlate with a transcriptional activity for that element, and whether all CCAAT elements only bind C/EBP. As Applicants have discussed above, the combined references cited by the Examiner simply do not teach one of skill in the art that the two CCAAT elements in the HL promoter are involved in regulating the transcriptional activity of HL and that these two elements bind C/EBP.

In light of the above arguments, Applicants respectfully assert that this rejection under 35 U.S.C. § 103(a) has been erroneously applied and respectfully request that it be reconsidered and withdrawn.

(ii) Claims 26-28 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Calkhoven *et al.* (*Eur. J. Biochem.* **249**:113-120, 1997) in view of Ameis *et al.* (*J. Biol. Chem.* **265**:6552-6555, 1990), further in view of Norris *et al.* (*J. Biol. Chem.* **270**:22777-22782, 1995), and further in view of Harnish *et al.* (*J. Biol. Chem.* **273**:9270-9278, 1998) (*see,* Office Action, paragraph bridging pages 6-7).

The Office Action relies on Calkhoven, Ameis, and Norris for the reasons described in the § 103(a) rejection above. Harnish is relied on to purportedly show that ERα or ERβ had been known before the effective filing date of the instant application (*see,* Office Action, page 7, fifth paragraph).

The Office Action alleges that it would have been obvious to one of ordinary skill in the art to make and use recombinant cells containing the three claimed DNA constructs with a reasonable expectation of success by using ERα or ERβ since one skilled in the art in making the claimed recombinant cell is very high (*see,* Office Action, paragraph bridging pages 7-8).

Applicants respectfully aver that Harnish does not remedy the multiple deficiencies of the other references detailed above. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants aver that all grounds of rejection of claims 26-42 have been overcome. Accordingly, Applicants respectfully request reconsideration and allowance of the claims of the instant application. If the Examiner believes that any further discussion of this communication would be helpful, the Examiner is encouraged to contact the undersigned at the phone number listed below.

Applicants petition for a two-month extension of time to respond to the outstanding Office Action. Applicants request that the extension of time fees be charged to our Deposit Account No. 08-0219. No additional fees are believed to be due in connection with this communication. However, if any additional fees are due, please apply any additional charges, or credit any overpayment, to our Deposit Account No. 08-0219.

Respectfully submitted,

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APPENDIX A

Comparison of putative C/EBP recognition sequences in Ameis *et al.* with the confirmed C/EBP sequences in Calkhoven *et al.*

Consensus:	5′ – N N **T K** N N **G** N **A A K** N – 3′, where K= T/G	(Calkhoven *et al.*)
Optimal:	N A **T T** G C **G** C **A A T** N	(Calkhoven *et al.*)
D site:	G A **T T** T G **G** T **A A T** G	(Calkhoven *et al.*)
B2 site:	T C **T T** T T **G** C **A A G** C	(Calkhoven *et al.*)
B1 site:	A A **T G** G C **G** A **A A C** A	(Calkhoven *et al.*)
F site:	G T **T T** A T **G** A **A A G** G	(Calkhoven *et al.*)
Ameis 1:	A A c **T** T C c C **A A T** G	(Ameis *et al.*)
Ameis 2:	G C a **T** C A c C **A A T** T	(Ameis *et al.*)

Sources of Sequences: 1. Calkhoven *et al.*, page 115

2. Ameis et al., page 6554